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## Brief Commentary

## Psychoneuroimmunology and cancer: A decade of discovery, paradigm shifts, and methodological innovations

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## ABSTRACT

This article introduces the supplement *Advances in Cancer and Brain, Behavior, and Immunity* and outlines important discoveries, paradigm shifts, and methodological innovations that have emerged in the past decade to advance mechanistic and translational understanding of biobehavioral influences on tumor biology, cancer treatment-related sequelae, and cancer outcomes. We offer a heuristic framework for research on biobehavioral pathways in cancer. The shifting survivorship landscape is highlighted, and we propose that the changing demographics suggest prudent adoption of a life course perspective of cancer and cancer survivorship. We note opportunities for psychoneuroimmunology (PNI) research to ameliorate the long-term, unintended consequences of aggressive curative intent and call attention to the critical role of reciprocal translational pathways between animal and human studies. Lastly, we briefly summarize the articles included in this compilation and offer our perspectives on future research directions.

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## 1. Introduction

In 2002, the National Cancer Institute (NCI), in collaboration with other Institutes and Centers of the National Institutes of Health, convened a meeting of scientific experts to discuss seminal research on behavioral, neural, endocrine, and immune system interactions in health and disease. To inform the development of a biobehavioral research agenda in cancer control, knowledge was extracted from contemporary studies of neuroimmune mechanisms of subjective experiences (e.g., stress, loneliness, and pain), biological processes (e.g., circadian rhythmicity, sleep, wound healing, sickness behavior, and apoptosis), and disease outcomes (e.g., human immunodeficiency virus, depression, and post-traumatic stress disorder). *Brain, Behavior, and Immunity* published the *Biological Mechanisms of Psychosocial Effects on Disease* supplement in February 2003. This seminal volume captured state-of-the-science reviews and commentaries by leading experts in psychoneuroimmunology (PNI) and served as a catalyst for biobehavioral<sup>1</sup> research

conducted in a cancer context. In the decade prior to the NCI commissioned supplement, *Brain, Behavior, and Immunity* published only 12 cancer-relevant articles. Since the 2003 supplement, the journal has featured 128 cancer-relevant papers that have generated 3361 citations (data from SCOPUS, retrieved November 1, 2012), relative to 55 papers on PNI and cancer, published in other peer review journals during the same time period. These bibliometric data highlight *Brain, Behavior, and Immunity* as a leading scholarly outlet for research on the biology of psychological and social experiences and the integrated mechanisms associated with cancer as a complex disease process. The current volume celebrates the 10-year anniversary of the 2003 supplement. This collection of invited reviews and research articles captures important discoveries, paradigm shifts, and methodological innovations that have emerged in the past decade to advance mechanistic and translational understanding of biobehavioral influences on tumor biology, cancer treatment-related sequelae, and cancer outcomes.

## 2. Transition from cellular immunity in peripheral blood to tumor-relevant measurements

Early clinical investigations focused almost exclusively on psychosocial modulations of the humoral and cellular immune response and, to some extent, on DNA repair (Andersen et al.,

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<sup>1</sup> For the purpose of this introduction, we use the terms “biobehavioral” and “psychosocial” interchangeably.

1994; Antoni, 2003; Kiecolt-Glaser and Glaser, 1999; Kiecolt-Glaser et al., 2002). Women at an increased genetic risk for cancer exhibited specific immune impairments and abnormalities in their endocrine response to stress (Bovbjerg and Valdimarsdottir, 1993; Dettenborn et al., 2005; Gold et al., 2003). Clinical studies documented associations between depression, social support, and natural killer cell activity in breast cancer patients (Levy et al., 1987; Levy et al., 1985; Levy et al., 1990). Other research groups observed distress/stress and social isolation-associated impairments in immune function among breast, cervical and ovarian patients (Andersen et al., 1998; Antoni et al., 2009; Lutgendorf et al., 2005; Nelson et al., 2008; Sephton et al., 2009; Thornton et al., 2007); however, the prognostic relevance of these associations remained uncertain (Cohen and Rabin, 1998). Building on the clinical significance of immune cells in ascites (Lotzova et al., 1986; Lotzova et al., 1984) and tumor-infiltrating lymphocytes (Lai et al., 1996) in ovarian cancer, Lutgendorf and colleagues observed significant associations between psychosocial factors and the cellular immune response at the tumor level in a clinical sample (Lutgendorf et al., 2005). This study, among others, signaled an important contextual transition for PNI studies of cancer, a transition aligned closely to advances in cancer cell biology and emerging appreciation for target tissues and the context in which tumors thrive (Marx, 2008).

### 3. Emergence of the tumor microenvironment

DeVita and Rosenberg (2012) recently chronicled significant discoveries and major events in cancer research since the founding of the *New England Journal of Medicine* nearly 200 years ago (DeVita and Rosenberg, 2012). Basic understanding of cancer biology has matured substantially beyond Virchow's observation of the cellular origin of cancer and the view of tumors as "insular masses of proliferating cancer cells" (p. 646, Hanahan and Weinberg, 2011). Progress has been led by milestones<sup>2</sup> like 'observations from a ploughman' (Dell, 2006; Hart and Fidler, 1980; Paget, 1889), 'bloodlines' (Farrell, 2006; Folkman, 1971), 'environmental awareness' (Schuldt, 2006), and the 'hallmarks of cancer' (Hanahan and Weinberg, 2000, 2011). Cancers have come to be seen as inherently complex collections of heterogeneous pathologies that vary by tissue of origin and constellation of genomic, proteomic, and metabolic alterations (Fidler, 2003; Hanahan and Weinberg, 2000, 2011; Vogelstein and Kinzler, 2004). Incipient mutated cells must acquire several biological capabilities to reach full malignancy, and several environments – i.e., the primary, invasive and metastatic tumor microenvironments – are created during tumorigenesis (Hanahan and Weinberg, 2011). In the case of solid tumors, commonly derived from epithelial cells, these microenvironments provide a safe haven for bidirectional communication between cancer cells and the tumor-associated stroma. Cells that construct the microenvironments include pericytes, cancer-associated fibroblasts, endothelial cells, local and bone marrow-derived stromal stem and progenitor cells, cancer stem cells, invasive cancer cells, and immune inflammatory cells (Albini and Sporn, 2007; Joyce, 2005; Joyce and Pollard, 2009; Langley and Fidler, 2007; McAllister and Weinberg, 2010; McCawley and Matrisian, 2001). Inflammation, a seminal biological process in the onset and progression of many diseases (Haroon et al., 2012; Nathan, 2002), has emerged as an essential enabling process for tumor growth and metastasis (Hanahan and Weinberg, 2011; Mantovani, 2009). Cytokines, chemokines, macrophages, and leukocyte infiltrates contribute to tumor progression by promoting invasion, migration, and angiogenesis (Gonda et al., 2009; Mantovani et al., 2008; Medrek et al., 2012; Pitroda et al., 2012; Solinas et al., 2009). Truly, it takes a village of distinct cell types and signaling systems to support the tumor ecosystem.

### 4. The central nervous system as a master regulator: implications for cancer

Renewed appreciation of the landscapes that enable tumor growth and metastatic dissemination inspire broader consideration of the macro-physiological milieus that potentially shape individual variability in the natural course of cancer and responsiveness to therapies (Castano et al., 2011; Schuller and Al-Wadei, 2010). We offer the following perspective (Fig. 1). The brain, as an adaptive and dynamic synthesizer of experiential and perceptual processes (Ganzel et al., 2010), can participate in the complex regulation of signaling systems used by the diverse array of cells and structures to enable tumorigenesis. Experimental and clinical studies suggest that downstream activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis exerts selective physiologic pressures that initiate molecular signaling pathways involved in DNA repair, angiogenesis, cell survival, inflammation, invasion, metastasis, and resistance to therapy (Antoni et al., 2006; Cole and Sood, 2012; Hara et al., 2011; Lutgendorf and Sood, 2011; Wu et al., 2004). Catecholamines (epinephrine, norepinephrine, dopamine) bind to  $\alpha$ -adrenergic receptors ( $\alpha$ -ARs) and  $\beta$ -adrenergic receptors ( $\beta$ -ARs), and acetylcholine binds to families of nicotinic (nAChRs) and muscarinic (mAChRs) receptors found on tumor cells and stromal compartments within the microenvironment (Schuller, 2008). Neuroendocrine receptor-mediated signaling has the documented ability to regulate leukocyte gene expression, molecular processes, and functional characteristics of cells within microenvironments (Badino et al., 1996; Cole and Sood, 2012; Lutgendorf et al., 2003; Lutgendorf et al., 2009; Schuller and Al-Wadei, 2010). Examples of observed effects include promotion of tumor cell growth, migration and invasive capacity, and stimulation of angiogenesis by inducing production of pro-angiogenic cytokines. Neuroendocrine hormones activate oncogenic viruses and alter several aspects of immune function, including antibody production, cell trafficking, and the production and release of proinflammatory cytokines (Glaser and Kiecolt-Glaser, 2005; Webster Marketon and Glaser, 2008). Although not explicitly reflected in our conceptual schema, peripherally generated inflammatory and other innate immune mediators can signal back into the central nervous system, stimulate afferent nerves that produce local cytokines, change neuronal function, and cause sickness behaviors as an adaptive response to systemic pressures (Dantzer and Kelley, 2007; Dantzer et al., 2012; Dantzer et al., 2008; Irwin and Cole, 2011; Kelley et al., 2003; Miller et al., 2008). Immune-to-brain communication cascades are thought to undergird cancer and treatment-related symptoms such as fatigue, depression, cognitive dysfunction, and sleep disturbance (Bower et al., 2011; Dantzer et al., 2012; Lutgendorf and Sood, 2011; Miller et al., 2008). Contemporary PNI remains poised to elucidate the prevalence, impact, and etiologies of cancer-related physical and affective sequelae at different phases of cancer survival (Bower, 2012; Dantzer et al., 2012; Haroon et al., 2012).

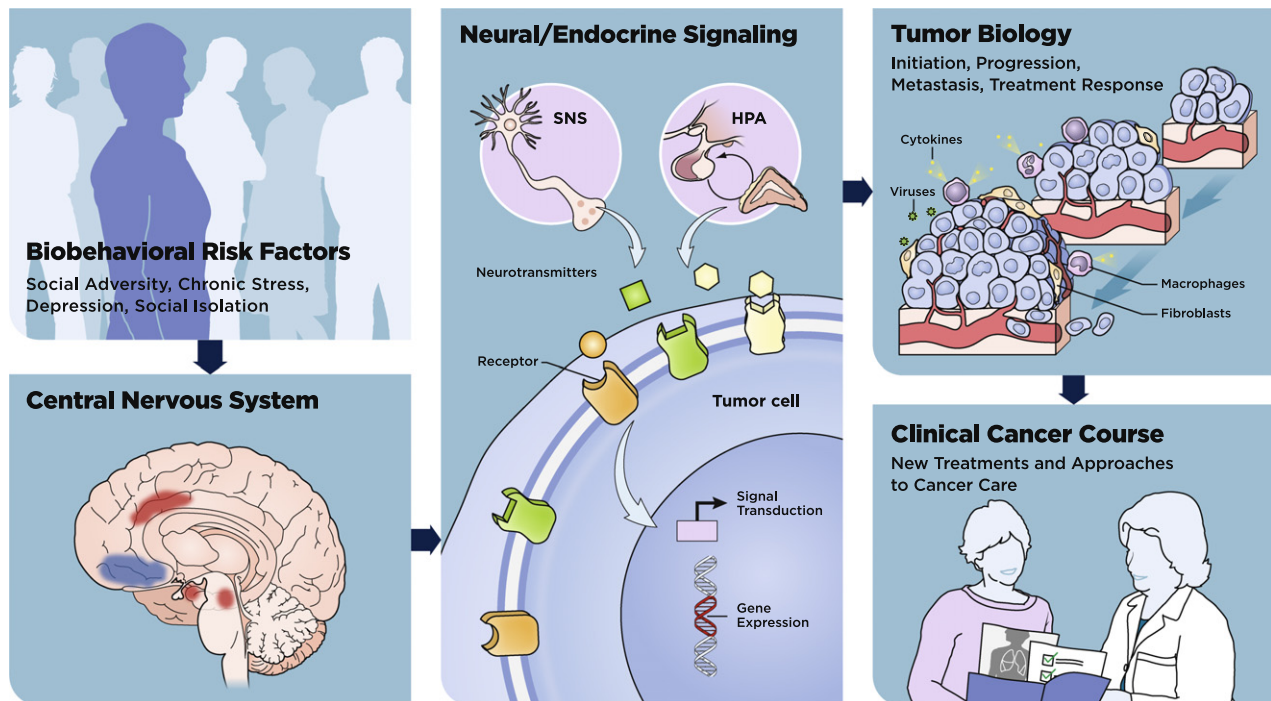
### 5. Shifting sands of survivorship

Advances in prevention, detection, and treatment (DeVita and Rosenberg, 2012) continue to yield significant declines in the incidence of most cancers and death rates for all cancers combined (Eheman et al., 2012; Siegel et al., 2012b). These trends, combined with overall increases in life expectancy, have created a "booming [aging] cancer survivor population" (p. 1996, Parry et al., 2011). Siegel et al. estimated 13.7 million American cancer survivors were alive in January 2012<sup>3</sup> (Siegel et al., 2012b). The majority

<sup>2</sup> See [http://www.nature.com/milestones/milecancer/pdf/milecancer\\_all.pdf](http://www.nature.com/milestones/milecancer/pdf/milecancer_all.pdf).

<sup>3</sup> Number of survivors projected to increase to nearly 18 million by 2022.

# Biobehavioral Pathways in Cancer



**Fig. 1.** Heuristic framework for research on biobehavioral risk factor influences on clinical cancer course.

of this emergent demographic had far exceeded the 5-year survival benchmark. Adolescent and young adult (AYA) survivors, diagnosed at ages 15 to 29 years, have an 82% probability of survival 30 years from diagnosis (Mertens et al., 2008). While this statistic is impressive, seminal research by Oeffinger, Lipshultz and others document profound adverse long-term health-related outcomes following exposure to highly aggressive curative intent therapies (Lipshultz et al., 2012; Oeffinger et al., 2006). Most notably relevant to PNI, childhood cancer treatments are associated with late effects on the cardiovascular, central nervous, endocrine, and immune systems. Further, survivors of adult, AYA, and pediatric cancers are at risk for recurrence and subsequent malignancies. Relative to the US population, survivors experience excess morbidity and mortality due to cardiac and vascular abnormalities and pulmonary complications (Choi et al., 2011; Mariotto et al., 2007; Oeffinger and Tonorezos, 2011; Siegel et al., 2012a; Valdivieso et al., 2012). This landscape highlights an opportunity to use PNI paradigms to understand cancer from a competing risk perspective in which multiple factors concurrently affect risks for morbidity and mortality (Mell et al., 2010; Schairer et al., 2004). Although not consistently observed (Zucca et al., 2012), age at diagnosis, general life expectancy trends, and long-term physiological sequelae of treatment exposure have converged to increase the prevalence of comorbidity or multimorbidity<sup>4</sup> in a cancer context (Braithwaite et al., 2012; Land et al., 2012; Patnaik et al., 2011; Ritchie et al., 2011; Yood et al., 2012).

<sup>4</sup> Multimorbidity is defined by the simultaneous existence of more than one pathophysiologic condition or clinical entity (p. 371; Ritchie et al., 2011).

## 6. Biobehavioral risk factors in the context of cancers as chronic diseases

Early prevention, detection, and treatment advances have shifted our conceptualization and management of most cancers from acute to chronic disease models, which are often modulated by psychosocial factors (Karelina and DeVries, 2011; Sullivan et al., 2012; Williams, 2008; Wyman et al., 2012). This paradigm shift further fuels our interest in psychosocial contributions to intra-individual variability in cancer outcomes. Meta-analytic reviews suggest stressful life experiences and depression are associated with poorer survival and higher mortality across a diverse array of cancer types (e.g., breast, lung, head and neck, hepatobiliary, lymphoid, and hematopoietic cancers) (Chida et al., 2008; Pinquart and Duberstein, 2010; Satin et al., 2009). Prospective endorsement of depressive symptoms, and cortisol slope were associated with decreased survival in patients with metastatic renal cell carcinoma (Cohen et al., 2012). Conversely, among women with metastatic breast cancer, a decline in depressive symptoms conferred survival benefit (Giese-Davis et al., 2011). A recent meta-analysis found the influence of social relationships on mortality comparable to risk conferred by tobacco and alcohol use. Further, the social relationship risk for mortality exceeded risks associated with physical activity (or lack thereof) and obesity (Holt-Lunstad et al., 2010). Inflammation often mediates associations between close relationships, depression, and chronic stress, and health (Kiecolt-Glaser et al., 2010). Extending prior cross-sectional findings of social support, depression and inflammatory gene expression associations, ovarian cancer patients with a greater sense of social attachment had a lower likelihood of death (Lutgendorf et al., 2012). Lastly, perceived social isolation or loneliness



predicts morbidity and mortality risk across different age groups (Perissinotto et al., 2012; Udell et al., 2012).

## 7. Bioecological perspective of cancer and cancer survivorship

These data highlight the potential utility of life course/life span or 'bioecological' perspectives of cancer and cancer survivorship. Most models of mortality and survival rely on tumor characteristics and treatment exposure as prognostic indicators (Merletti et al., 2011; Ward et al., 2004; Wei et al., 2010). Tumors develop within microenvironments, yet cancers develop within a person nested within several environmental contexts. Colditz and Wei (2012) assert that traditional projections of cancer mortality fail to account adequately for multilevel interactions and reciprocity among biologic pathways, physical/built environment, and social/behavioral factors (Colditz and Wei, 2012). Models that dynamically capture exposure to multiple risk and protective factors, certain to have pleiotropic effects across and within time and levels of analysis (Evans and Kim 2010), promise to reveal greater understanding of individual- and population-level differences in cancer risk and outcome (Gehlert et al., 2008; Hiatt and Breen, 2008; Warnecke et al., 2008). Inequalities in cancer incidence, mortality, and survival by race/ethnicity and socioeconomic status prevail<sup>5</sup> (Chang et al., 2012; Merletti et al., 2011; Ward et al., 2004). A growing literature defines the biology of [social] disadvantage and early adversity and offers tenable hypotheses and mechanistic pathways as explanations for disparities in health and disease outcomes across the lifespan (Adler and Stewart, 2010; Boyce et al., 2012; Kelly-Irving et al., 2012). We use this platform to encourage deliberate investment in research on biopsychosocial mechanisms associated with persistent disparities in cancer outcome (Parente et al., 2012).

## 8. Animal models of human disease: powerful tools for elucidation of mechanisms

Use of correlation studies to support 'weight of the evidence' has been a prevalent criticism levied against PNI studies of cancer. However, within the last decade, growing availability of transgenic and knockout mouse models of human cancer provides opportunities to understand how PNI-type interactions may modulate the molecular biology of cancer. Orthotopic and human tumor xenograft models more accurately recapitulate the dynamics of human cancer *in vivo* (Talmadge et al., 2007). Biologically sophisticated animal models of human cancer provide a context for experimental manipulation of psychosocial factors, such as environmental enrichment (Cao et al., 2010), isolation (Hermes and McClintock, 2008), stress (Sheridan et al., 2004; Thaker et al., 2006), and depression (Lamkin et al., 2011). In addition, animal models advance the discovery of the consequent changes in neuronal structure and function, neuroendocrine and immune activity, and peripheral biology that influence tumor cells and their microenvironment. In this conceptualization, psychosocial factors set the stage for a "macroenvironment" that can shape tumor microenvironments to be more or less favorable to tumor growth. This systems-approach highlights the interactions of networks of pro-tumor and anti-tumor mechanisms, and underscores the multiple processes involved in both biobehavioral contributions to tumor growth, as well as in resistance to tumor growth. Such a broad,

integrative approach will be necessary for the next steps in research that target both mechanisms and interventions.

## 9. Overview of invited reviews and empirical reports in *Advances in Cancer and Brain, Behavior, and Immunity*

Scholars in PNI and related disciplines and in cancer research were invited to author the papers contained in this volume. Reflective of the decade that bore witness to the sequencing of the human genome, the Cole review highlights several conceptual and methodological innovations that are transforming our knowledge of neural and endocrine regulation of the cancer genome (Cole, 2013). Sood and colleagues review studies that have converged to refine our understanding of sympathetic nervous system regulation of pathways relevant to cancer growth and progression (Armaiz-Pena et al., 2012). The nuanced and selective influences of neuroendocrine hormones on tumor cells, stromal cells and the metastatic cascade have come into focus and are beginning to reveal new therapeutic opportunities. Volden and Conzen present a complementary review of the influence of glucocorticoid signaling on tumor progression through cell context-specific transcriptional networks (Volden and Conzen, 2012 1045). In the clinical context, disruption of HPA rhythms, as indicated by diurnal cortisol slopes, predicted early metastatic breast cancer mortality (Sephton et al., 2000). Sephton and colleagues, as reported in this volume, replicate those findings in a small sample of lung cancer patients followed for a median of 4 years from date of diagnosis (Sephton et al., 2012). Volden and Conzen foreshadow emerging interest in stress regulation of epithelial cancer biology through metabolic pathways and energy regulators such as insulin, leptin, ghrelin, and adiponectin (Cao and During, 2012; Williams et al., 2009).

Convergence of animal models and human correlative studies led Neeman and Ben-Eliyahu to identify catecholamine and prostaglandin-mediated immunosuppression as a perioperative risk factor for cancer recurrence and metastasis (Neeman and Ben-Eliyahu, 2012). The authors advance a theoretical model that captures the cumulative risk and review mechanistic support for the use of pharmacological blockade of key mediators during the perioperative period. Sheridan and colleagues review the utility of a mouse model of repeated social defeat to elucidate neural-immune mechanisms in cancer (Powell et al., 2012). This review highlights the role of myeloid-derived cells in stress-primed inflammation, in tissue remodeling in non-immune and immune organs, and in support of behavioral states experienced as cancer-associated sickness behaviors (see reviews in this volume by Bower and Lamkin, 2012; Costanzo et al., 2012; Irwin et al., 2012). The empirical paper by Madden et al. examines the impact of social isolation on breast cancer pathogenesis in adult severe combined immunodeficiency mice using a human breast cancer cell line known to express  $\beta$ -ARs (Madden et al., 2012). The results raise implications of mild vs. chronic stress exposure, timing of exposure during the life span of experimental animals, and the need to capture transient shifts in target cell populations. Further, the study supports the importance of myeloid-derived suppressor cells and stress-associated leukocyte recruitment as indicated by changes in macrophage populations in tumor and spleen, similar to that observed with social disruption (SDR) stress paradigms (Engler et al., 2004; Powell et al., 2012).

Bower and Lamkin identify two questions that direct contemporary research on cancer-related fatigue, i.e., what are the neural underpinnings of fatigue that are distinct from depression, and what are the factors that contribute to inflammation and fatigue at different treatment phases (Bower and Lamkin, 2012)? The review calls for established animal models of cancer-related fatigue, attention to signal transduction pathways and downstream mark-

<sup>5</sup> Social ecological theory predominately guides the exploration of the fundamental causes of disparities in health. A thoughtful and balanced reflection of the relative contributions of local, State, and Federal level policies, social and physical environments, and access to and quality of health services is beyond the scope of this commentary and research contained in this volume. For recent reviews and perspectives see; Colditz et al., 2012 and Esnaola and Ford, 2012.

ers of inflammatory activation, prospective longitudinal studies of fatigue to map time course and recovery, and exploration of mechanisms that might explain observations of symptom clusters. The authors suggest early life stress as a plausible risk factor for inflammation that undergirds cancer-related fatigue. The empirical paper by Witek-Jansek et al. in this volume explores whether childhood adversity is associated with vulnerability for intense sustained behavioral symptoms, including fatigue and depressive symptoms, and quality of life and immune dysregulation (Witek-Janusek et al., 2012).

Irwin and colleagues describe the common presentation of sleep disturbance and depression in cancer survivors (Irwin et al., 2012). The authors outline a model in which sleep disturbance drives alterations in inflammatory biology, which result in depressive symptoms and in clinical depression for some. The model acknowledges depression history and other psychosocial, biobehavioral, and medical factors that might act as moderators. The Lutgendorf laboratory contributes an analysis of associations between cortisol, interleukin-6, depression, fatigue, and disability in ovarian cancer patients followed prospectively from pre-surgical baseline to one-year post surgery, and illustrates how chemotherapy acts to normalize these biological markers (Schrepf et al., 2012).

Although challenges exist, the review by Costanzo et al. identifies opportunities to explore clinically significant PNI relationships in a hematopoietic stem cell transplantation context (HSCT) (Costanzo et al., 2012). Improved understanding of the factors that moderate timely immune recovery and optimal immune regulation might confer improved short- and long-term outcomes for HSCT recipients. Noted as challenges for PNI researchers working in a HSCT context are the pace of change and evolution in HSCT medicine and associated technical innovations. The secondary data analysis by McGregor et al. investigating the effect of pre-transplantation distress on white blood cell count among autologous hematopoietic cell transplantation patients, highlights these challenges (McGregor et al., 2012).

Within the last decade, exercise has been established as an effective adjuvant therapy to control adverse consequences associated with cancer treatment. Jones et al. comprehensively reviews extant evidence linking exercise behavior, functional capacity/exercise capacity, disease recurrence, and cancer-specific and all-cause mortality (Betof et al., 2012). Further, the authors outline host and tumor-related mechanisms underlying the exercise/fitness and prognosis relationship and review evidence from pre-clinical animal models of cancer. This exciting work highlights exercise as one critical component of energy balance influences on cancer etiology, progression, and outcome (Hursting et al., 2012).

This volume would not be complete without a balanced synthesis of extant literature on psychological and physiological adaptation and psychosocial interventions following a diagnosis of cancer (Antoni, 2012). Antoni notes the opportunity to consider outcomes beyond survival and disease recurrence, the importance of determining optimal timing of interventions, acknowledgment of cancers as different diseases, and the need to identify individuals at high risk for poor outcomes. He discusses application of microarray and bioinformatic analyses (Cole, 2010; Cole et al., 2005) to demonstrate that an intervention can causally influence inflammatory and metastasis-regulated gene expression in circulating leukocytes from early-stage breast cancer patients (Antoni et al., 2012).

Three empirical papers in this volume focus on cognitive dysfunction due to cancer treatment exposure in breast cancer samples (Ganz et al., 2012; Kesler et al., 2012; McDonald et al., 2012). Ganz et al. conducted an interim cross-sectional analysis of a prospective, longitudinal, observational cohort study to explore associations between proinflammatory cytokines, cerebral functioning, and chemotherapy exposure (Ganz et al., 2012). Similarly, Kesler and colleagues investigated the correlations between

hippocampal volume and peripheral cytokine levels in a sample of breast cancer survivors nearly five years post-chemotherapy exposure (Kesler et al., 2012). The Kesler et al. and Ganz et al. papers report associations between tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and memory impairments. McDonald and colleagues replicate and extend prior work by their group and others (Kesler et al., 2011; McDonald et al., 2010). Their current study reports chemotherapy-associated structural brain changes in frontal regions that correspond to concurrent perceptions of compromised executive function (McDonald et al., 2012). We recognize that these studies have limitations such as small samples sizes, discordance between objective cognitive performance and subjective complaints, and, in some cases, lack of pre/post-treatment and/or non-cancer control comparisons. These limitations beg for prospective longitudinal designs that facilitate pooling of data from different research groups, harmonization of measures, and the use of advanced statistical methods and modeling (Nelson and Suls, *in press*). Nevertheless, research presented by Ganz et al., Kesler et al., and McDonald et al. nicely illustrates the nexus of brain, behavior, and inflammation.

## 10. Through the looking glass

This supplement synthesizes contemporary understanding of PNI in a cancer context and suggests opportunities for further discovery of mechanisms and development of interventions to improve clinical cancer care. Multiple signaling pathways by which the “macroenvironment” can influence the tumor microenvironment are identified, but many unanswered questions remain. For example, numerous effects of catecholaminergic and glucocorticoid signaling on tumor growth and progression have begun to be mapped, but it is likely that there are multiple downstream effects on tumor growth processes, many of which have not been identified (for example, see Zappala et al., 2012). Hanahan and Weinberg (2011), in an update to their classic paper, highlighted 10 hallmarks of cancer that are necessary for tumor growth and progression. These include sustaining proliferative signaling; evading growth suppressors; avoiding immune destruction; enabling replicative immortality; tumor-promoting inflammation; activating invasion and metastasis, inducing angiogenesis; genome instability and mutation; resisting cell death; and deregulating cellular energetics. The work highlighted in this issue describes how the stress response can influence the macroenvironment to support these hallmarks.

In addition to effects on the tumor and microenvironment, there are likely multiple upstream biobehaviorally modulated pathways that may affect tumor growth, which will make productive targets for future investigation. These include the role of the parasympathetic nervous system, of biobehaviorally sensitive neuropeptides and hormones such as oxytocin, prolactin, growth hormone, and prostaglandins, as well as a variety of metabolic mediators (e.g. insulin growth factor-1, leptin, and ghrelin) that are sensitive to biobehavioral pathways. Biobehavioral mediators seldom work alone, and yet mechanistic research has focused on investigation of discrete pathways for the sake of defining mechanisms. However, to understand the relevant mechanisms, it will be important to understand downstream effects of interconnected pathways – e.g., the synergistic effects on tumor dynamics of NE and cortisol in chronic stress. We envision a complex web of systemic pathways that influence tumor growth and development at multiple levels. This critical information will guide understanding of whether therapies can be successful by blocking only adrenergic signaling (as in use of beta-blockers), or whether adrenergic signaling and prostaglandins must be jointly blocked (see Neeman and Ben-Eliyahu, 2012), or whether adrenergic and glucocorticoid

pathways must both be targeted. Understanding whether narrow or broad targeting of therapies is clinically indicated is critical in developing successful pharmacologic approaches. Behavioral interventions tend to be ‘broad spectrum’- targeting many overlapping biobehavioral pathways; future research on behavioral interventions may benefit from analysis of which molecular pathways are active.

Future research will also benefit from parsing out effects of different biobehavioral states – e.g. stress, depression, social isolation – to determine if there is one final common pathway, or to what extent there are discrete biological signatures of these different psychological constructs. Molecular signatures of positive constructs also need further investigation. For example, does resilience just mean less sympathetic activation or less hormonal and inflammatory responsivity to stress, or does it mean greater parasympathetic tone, or differential signaling of pathways such as those involving oxytocin or dopamine? Likewise, it is not known whether stress factors act in a relatively linear dose–response fashion or whether there are thresholds for stress/depression/social isolation that determine physiological trajectories that will influence the clinical course of cancer. These kinds of data will help us better understand who will most benefit from behavioral or pharmacological interventions to reduce adrenergic signaling or stress response states – for example, what levels of stress/distress are necessary at the outset for an intervention to make a difference. Moreover, the use of discrete interventions is useful for mechanistic research purposes, but it is possible that multifaceted total lifestyle interventions that address stress factors, as well as nutritional and exercise lifestyle components, will be necessary to profoundly impact cancer growth. To date, research on multimodal interventions remains quite limited.

Additionally, the effects of biobehavioral pathways on recovery from specific cancer treatments such as HSCT, adoptive immunotherapy, surgical recovery, are important frontiers for future work. Understanding tumor and treatment effects on the central nervous system are equally important. As reported by some of the papers in this volume, we are just beginning to understand the relevant biology in post-chemotherapy fatigue and cognitive difficulties – this type of mechanistic understanding is critical before new treatments can be developed and tested.

Future directions also include determination of what are the most important intermediate outcome variables for biobehavioral cancer research. In addition to overall survival and progression-free survival, to what extent are gene signatures, metabolomics, and epigenetic changes important outcomes for this work? The research in this volume points to the dramatic discoveries that have been made in the last decade to define this field. Future research holds promise for discovery of novel biobehavioral signaling pathways that are relevant to cancer and a greater understanding of behavioral, pharmacologic, and complementary interventions that target these mechanisms.

In conclusion, we would be remiss if we did not thank lead authors and their authorship teams for contributing scientific advances relevant to this volume. These individuals and many others have worked quite tirelessly to improve methodological rigor, establish causation as appropriate, collaborate in the spirit of transdisciplinary team science, and move between different research designs to test and confirm experimental and clinical findings. We thank the many scholars who engaged in the peer review process to vet the invited mini-reviews and empirical papers that comprise this supplement. We acknowledge the inspiration and contributions of the National Cancer Institute Network on Biobehavioral Pathways in Cancer<sup>6</sup> and the invaluable support of

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## Conflict of interest

The authors of this manuscript have nothing to declare.

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